REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following reasons.

I. Status of the Claims

Claims 3, 10, 23, 24, 37, 41, 45, and 49 were previously cancelled. Claims 5-7 and 32 are cancelled in this response without prejudice or disclaimer thereof. Applicants reserve the right to pursue the subject matter of any cancelled claim in one or more continuing applications.

Claims 1 and 35 have been amended to recite the transitional phrase "consisting of" regarding the ingredients of the composition of the claimed invention. Claims 30 and 35 have been amended to be consistent with the recitations of claim 1.

Applicants acknowledge the finality of the outstanding Office Action. The claim amendments: (i) do not introduce any new matter; (ii) are made to cancel claims and to narrow the scope of the existing claims by replacing the open-ended transitional phrase "comprising" with the closed-ended transitional phrase "consisting of"; (iii) conform with the formality requirements by reciting consistent language in the independent claims; and (iv) place the application in condition for allowance or at least in better condition for appeal. Therefore, Applicants respectfully request entry of the claim amendments. Upon entry, claims 1, 2, 4, 8, 9, 11-22, 25-31, 33-36, 38-40, 42-44, 46-48, and 50-54 will be pending.

II. Rejection of Claims under 35 U.S.C. §103(a)

Claims 1, 2, 4-9, 11-22, 25-36, 38-40, 42-44, 46-48, and 50-54 are rejected under 35 U.S.C. §103(a) for allegedly being obvious over U.S. Patent No. 5,552,160 to Liversidge et al. ("Liversidge") in view of U.S. Patent No. 6,093,420 to Baichwal et al. ("Baichwal"). Applicants respectfully traverse the rejection.

A. Liversidge fails to proffer a teaching, suggestion, or motivation to combine the cited references.

According to the Examiner, the claimed invention is rendered obvious by the combination of the cited references because Liversidge allegedly teaches a nanoparticulate active agent composition comprising a surface modifier adsorbed on the surface thereof, and Baichwal allegedly teaches a sustained release dosage form. *See* final Office Action, pages 2 and 3.

The Examiner further asserts that Liversidge provides a teaching, suggestion, or motivation to combine the references, thereby obtaining a controlled release dosage form of the nanoparticulate active agent composition, because "Liversidge teaches coating the drug particle with the claimed surface stabilizer and the claimed rate controlling polymer." Final Office Action, page 4, 1st full paragraph.

In fact, Liversidge *does not* teach any rate controlling polymer coating the drug particles as the Examiner asserts. Liversidge is also silent as to obtaining a controlled release formulation. Although some compounds encompassed by the surface stabilizer of Liversidge's composition overlap those of the high molecular weight rate controlling polymer of the claimed invention, Liversidge does not disclose that these compounds form a matrix to "bury" the active agent particles having a surface modifier adsorbed on the surface thereof. In the absence of this structural feature of forming a rate controlling matrix, the compounds disclosed by Liversidge as surface stabilizers will not function to sustain the release of the active agent. Therefore, Liversidge fails to provide a teaching, suggestion, or motivation to obtain a controlled release formulation as the Examiner contends.

B. Baichwal fails to teach the same rate controlling polymers as prescribed by the claimed invention.

The Examiner contends that "Baichwal teaches the use of the same rate controlling polymers to obtain a sustained/controlled release composition," with reference to column 7, line

65, through column 8, lines 1-8. The cited passage discloses exemplary gelling agents that "may optionally be included" in Baichwal's formulation.

However, the Examiner fails to acknowledge that Baichwal's formulation requires the presence of two essential ingredients, xanthan gum and a crosslinking agent, in a certain ratio, such as from 1:20 to 20:1. The crosslinking agent can be a galactomannn, such as locust bean gum. *See* column 2, lines 38-47. These two ingredients are *essential* in Baichwal's formulation because Baichwal describes that the desired release profile "is caused by the 'swelling' and 'gelling' properties of the xanthan gum and the cross-linking agent upon exposure to an environmental fluid." Column 5, line 65, through column 6, line 3. In contrast, the claimed invention does not require the presence of xanthan gum or locust bean gum, as indicted by the recited ingredients and the closed-end transitional phrase.

The Examiner misunderstood Applicants' prior arguments regarding Baichwal's release profile. *See* Office Action, at page 5, 2nd full paragraph. Applicants pointed out in the prior response that to achieve the desired release profile, Baichwal requires the presence of two essential ingredients, xanthan gum and locust bean gum, which are not included in Applicants' claimed invention. Therefore, the combined teachings of the cited references fail to meet all recitations of the claims.

C. It is non-obvious to obtain the claimed invention, particularly in view of the state of the art.

Nanoparticulate formulation of active agents was known as of 1992, as disclosed in U.S. Patent No. 5,145,684, and controlled release formulations were known prior to 1992. Despite the fact that both concepts coexisted separately in the art for years before the date of the filing of the present application, the possibility of combining these two approaches was not recognized. This evidence mitigates against the arguments that it would have been obvious to combine the teachings of the cited references.

Furthermore, Applicants submit herewith a publication by Chen et al., "Challenges and New Technologies of Oral Controlled Release," *Oral Controlled Release Formulation Design and Drug Deliver: Theory to Practice*, edited by Hong Wen and Kinam Park, pages 257-276 (2010) (Exhibit 1). Exhibit 1 demonstrates that significant challenges exist even as of today in developing controlled release formulations for drugs with poor aqueous solubility (see the paragraph bridging pages 257 and 258). Aside from nanotechnology, there are numerous strategies employed such as salt formation, microenvironmental pH control, solubilisation with surfactants, complexation with cyclodextrin, solid dispersion, and lipid-based formulation (see page 257, 3rd paragraph and Table 16.1). Exhibits 1 concludes: "Many drugs need more complicated formulation approaches to enhance the dissolution, such as amorphous solid dispersion, emulsion, microemulsion, self-emulsifying, and nanoparticles. *Among them, amorphous solid dispersion is the most popular approach to enhancing solubility and dissolution.*" Page 258, at the top of the right column; emphasis added.

Accordingly, as of today, 20 years after nanoparticulate formulation was introduced, the use of nanotechnology in controlled release formulations for poorly soluble drugs is not a preferred approach by conventional wisdom. Concerning nanoparticulate formulations, Exhibit 1 comments as follows (emphasis added):

> *Nanoparticle formulation can be used to formulate poorly soluble drugs to enhance bioavailability. The drug dissolution rate is increased due to the increase of surface area.* ***However, there are barely any available literatures about the controlled release of poorly soluble drugs with nanoparticle as the carrier****. It is projected that an erosion-based system may be more suitable because the drug solubility is not changed. Diffusion-controlled matrix or membrane coating system is challenging to achieve the goal.*

Thus, in view of the state of the art, it was surprising, at the time of the invention, that a nanoparticulate composition of a poorly soluble drug could be formulated into a controlled release formulation.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16 - 1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: May 7, 2012

By 

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EXHIBIT 1

16

CHALLENGES AND NEW TECHNOLOGIES OF ORAL CONTROLLED RELEASE

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16.1 INTRODUCTION

As discussed in previous chapters, significant advances have been attained in developing and commercializing oral controlled release products. Many platforms are available for delivering small molecule drugs with good aqueous solubility in a prolonged release or a delayed release. However, there are significant challenges in developing controlled release formulations for drugs with poor aqueous solubility, which require both solubilization and engineering of release profile. To deliver drugs at zero-order release rate, preferably independent of the gastrointestinal (GI) tract environment, besides osmotic pump drug delivery systems, many efforts and achievements have been made.

Moreover, many of new therapeutics under development are large molecules such as peptides, proteins, oligonucleotides, and vaccines. Their physical, chemical, and biopharmaceutical attributes distinct from small molecule drugs demand novel controlled release technologies to diminish barriers for oral delivery, such as instability in GI tract and poor absorption. Those unmet technology needs create great opportunities for research, development, and innovation. It is optimistic that breakthroughs in controlled oral delivery for water-insoluble drugs and biopharmaceuticals will have a significant impact on pharmaceutical and biotechnology industry. On the other hand, the continuous improvement in current delivery technologies is also important regarding the decrease of cost and the increase of efficiency. Those advancements include novel excipients, processes, and equipments as new tools for formulation scientists to develop oral controlled release formulations.

16.2 ORAL CONTROLLED DELIVERY FOR WATER-INSOLUBLE DRUGS

With few exceptions, drug products have to be dissolved in GI fluids to get absorbed for small molecule drugs. For a water-insoluble drug, the absorption and bioavailability could be restricted by dissolution rate and solubility in the GI tract. There are many established approaches to formulating water-insoluble drugs as oral dosage forms. Strategies include salt formation, microenvironmental pH control, solubilization by surfactants, complexation with cyclodextrins, solid dispersion, lipid-based formulation, and nanoparticles formulation (Table 16.1). Which strategy to choose is based on molecular and physical properties of a drug. It demands substantial formulation and process development to have a drug product with enhanced bioavailability for a water-insoluble drug.

Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice, Edited by Hong Wen and Kinam Park

TABLE 16.1 Formulation Approaches for Water-Insoluble Drugs

Strategy	Mechanism	Practical Approach
Salt formulation	Ionization at solid state for ionizable compounds	HCl, citrate, maleate salt et al. for weak bases; sodium, potassium, lysine salt et al. for weak acids
pH control	Promote or maintain ionization during dissolution for ionizable compounds	Alkalizing agents such as sodium bicarbonate, calcium carbonate for weak bases; acidifying agents such as citric acid, tartaric acid for weak acids
Surfactant	Improve wettability and solubility	Sodium lauryl sulfate, Poloxamer
Complexation	Form complex with cyclodextrin to improve aqueous solubility	Sulfobutylether beta cyclodextrin, hydroxypropyl beta cyclodextrin
Solid dispersion	Formation and maintain amorphous state with enhanced solubility	*Process*: spray drying, melt extrusion. *Polymers*: povidone, polyethyleneglycol, polymethacrylate, hydroxypropyl methylcellulose, ethylcellulose, hydroxypropyl cellulose
Lipid-based formulation	Formation of emulsion, microemulsion to enhance solubility and dissolution	*Liquid or semisolid excipients*: propylene glycol monocaprylate, macrogol glycerides, glyceryl monooleate, medium-chain triglycerides, diethylene glycol monoethylether
Nanoparticles	Reduce particle size and enhance dissolution	*Process*: milling, controlled crystallization. *Excipients*: Tween, phospholipid, Poloxamer

Developing a controlled release formulation for a water-insoluble drug is very challenging. A controllcd oral delivery may be needed to achieve prolonged exposure or time-based release for a water-insoluble drug under certain circumstances. It could offer advantages in imporving efficacy, reducing side effect, or achieving a more desirable dose regimen. However, many platforms for controlled release have been established for drugs with acceptable aqueous solubility, which have been thoroughly reviewed in previous chapters. The release rate of a soluble drug in a solid dosage form is slowed down in a certain mode to achieve controlled release. It is clear that direct plug-in of current matrix-based or coating-based delivery systems without technology fabrication will fail to achieve acceptable controlled release of a water-insoluble drug. On the other hand, *in vitro* dissolution methods based on a sink condition generated by surfactants may provide misleading correlation for *in vivo* behaviors.

A combination of solubilization and modulating the release is needed to achieve controlled release for a water-insoluble drug. If a drug could be solubilized by a surfactant or a complex agent, inclusion of a solubilizing agent in polymer-based matrix tablets may provide a solution. Rao et al. studied the matrix tablet formulation of prednisolone, a sparingly water-soluble drug, using sulfobutylether-β-cyelodextrin (SBEBCD) as a solubilizing agent. SBEBCD promotes a sustained and complete release in a hydroxypropyl methylcellulose-based tablet formulation [1]. Another study also demonstrated that SBEBCD could also work as a solubilizing agent and an osmotic agent for controlled porosity osmotic pump pellets of prednisolone [2]. A complete and sustained release of prednisolone has been observed. It has been reported that controlled release felodipine tablets have been effectively prepared using Poloxamer as a solubilizing agent and Carbopol as a controlled release matrix [3].

Many drugs need more complicated formulation approaches to enhance the dissolution, such as amorphous solid dispersion, emulsion, microemulsion, self-emulsifying, and nanoparticles. Among them, amorphous solid dispersion is the most popular approach to enhancing solubility and dissolution.

There are numerous publications about the development of controlled release formulations of water-insoluble compounds using solid dispersion as a solubilization approach. For a solid dispersion, drug molecules are stabilized in a high-energy state with hydrophilic polymers such as polyethylene glycol, polyvinyl povidone, and polyvinyl alcohol. Solid dispersions could be prepared by spray drying or melting extrusion. Mehramizi has reported that an osmotic pump tablet of glipizide has been developed using glipizidc/polyvinylpyrrolidone dispersion as the core [4], where the solid dispersion has enhanced the solubility and ensured the complete release. Hong and Oh have studied the dissolution kinetics and physical characterization of three-layered tablets of nifedipine solid dispersion with poly(ethylene oxide) matrix capped by Carbopol [5]. They have discovered that the swelling and morphological change of Carbopol layers have minimized the release of rapidly erodible PEO200K (MW 200,000) and changed the nifedipine release to a diffusion-controlled process.

However, the physical stability of solid dipersions has to be monitored for polymer-based matrix systems, membranc coatings, or osmotic systems during prolonged release. All three approaches need water to diffuse inside formulation to solubilize drugs and advance the release. Drugs may crystallize out during the prolonged exposure to water due to

supersaturation inside dosage form or change of glass transition temperature because of interaction with water. New formulation approaches have to be undcrtaken to ensure the physical stability of solid dispersions and achieve sustained release, which will be discussed in Section 16.3.

Nanoparticle formulation can be used to formulate poorly soluble drugs to enhance bioavailability. The drug dissolution rate is increased due to the increase of surface area. However, there are barely any available literatures about the controlled release of poorly soluble drugs with nanoparticle as the carrier. It is projected that an erosion-based system may be more suitable beeause the drug solubility is not changed. Diffusion-controlled matrix or membrane coating system is challenging to achieve the goal.

16.3 NEW FORMULATION DESIGNS IN ACHIEVING DESIRED RELEASE PROFILES

Many formulation designs have been pursued to achieve controlled release and minimize the impact of the GI environment. Osmotic pump drug delivery systems pionecred by Alza have many proved successes regarding those two aspects, as covered in previous chapters. Disintegration-controlled matrix tablet (DCMT) and erodible molded multilayer tablet by Egalet take an erosion approach and show some promises. On the other hand, bioadhesive polymers have advantages in improving gastroretentive delivery and enhancing localized therapy in GI tract. Moreover, significant progress has also been made in using computer modeling to design controlled release formulations.

16.3.1 Disintegration-Controlled Matrix Tablet

DCMT is an erosion-based controlled relcase platform. It has been developed for the sustainecl release of solid dispersions by Tanaka et al. [6, 7]. Disintegration-controlled matrix tablets contain hydrogenated soybean oil as the wax matrix with solid dispersion granules uniformly distributed in the wax. The solid dispersion granules are formulated with low-substituted hydroxypropylcellulose as a disintcgrant. Drug release is controlled by the process of tablet erosion. The wax only allows the penctration of water to the surface layer of tablet, and water triggers the swelling of the disintegrant on the surface, and subsequently tablet erosion results in the separation of solid dispersion granulcs from the tablet. A constant rate of tablet disintegration/erosion can be achieved by repeating the processes of water penetration and swelling/separating of solid dispersion granules (Figure 16.1).

DCMT has been successfully applied to the sustained release formulation of nilvadipine [6], a poorly soluble drug with an aqueous solubility of 1 μg/mL. The release profile of nilvadipine from DCMT has been modified by balancing the amount of wax and the amount of disintegrant. The wax matrix prevented water penetration into the tablet and ensuresd the amorphous state of solid dispersion during the dissolution process. Sustained release profiles of nilvadipinc from DCMT were ncarly identical in several dissolution mediums with varying pH and agitation speed [6]. An *in vivo* study in dogs has revealed that DCMTs successfully sustained the absorption of nilvadipine without reducing the bioavailability compared with IR coprecipitate tablets [7] (Figure 16.2). It suggests that DCMT is able to achicve the complete dissolution and absorption of a poorly water-soluble drug by maintaining the physical stability of solid dispersion in the GI tract.

16.3.2 Erodible Molded Multilayer Tablet (Egalet®)

Similar to DCMT, Egalet erodible molded tablets is an crosion-based platform. It has the advantage of delivering

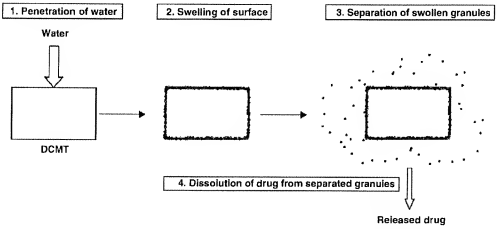

FIGURE 16.1 Proposed mechanism of drug release from DCMT [6].

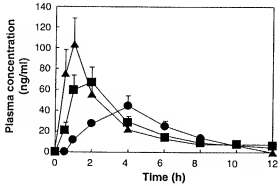

FIGURE 16.2 Plasma concentration profiles of nilvadipine after oral administration of DCMTs to beagle dogs under fasting condition [7]. key; (■) IR tablets, (■) DCMT-1, (●) DCMT-2.

zero-order or delayed release with minimal impact from the gastrointestinal conditions. Nevertheless, Egalet is a more sophisticated engineered delivery system with erosion occurred in one dimensional, whereas DCMT erosion is taken place in all three dimensions. It is obvious that Egalet could achieve a better zero-order release. Drug is dispersed in the matrix and the release is controlled by the rate of erosion in the two ends of tablets. The surface area for erosion is constant.

Egalet erodible molded multilayered tablets are prepared by injection molding (IM) [8]. As shown in Figure 16.3, a tablet produced via Egalet technology contains a coat and a matrix. Drug release is controlled through the gradual erosion of the matrix part. The mode and rate of release are designed and engineered by altering the matrix, the coat, and the geometry to achieve either a zero-order release or a delayed release.

For a zero-order release, a drug is dispersed through the matrix. The coat is biodegradable but has poor water permeability to prevent its penetration. The matrix tends to erode when in contact with available water. The erosion of the matrix is caused by GI fluids and promoted by gut movements in the GI tract. The drug release is mediated almost wholly by erosion because the dosage form is designed to slow down the water diffusion into the matrix. It is definitely more desirable for drugs with chemical and physical stability issues after contacting with water. For example, if the drug is solubilized as a solid dispersion and the solid dispersion tends to crystallize after interacting with water, the erosion-based delivery will ensure the stability. It is clear that Eaglet-based delivery system is suitable for the controlled delivery of water-insoluble compounds. The unique delivery system will also prevent hydrolysis and reduce luminal enzymatic activity.

As illustrated in Figure 16.3, the release rate of Egalet prolonged release is dependent on the erosion rate and drug concentration. It is clear that a zero-order release can be easily achieved if a uniform drug concentration in the matrix and a constant erosion rate are present. The erosion rate could be tailored through altering the composition of the matrix. For example, addition of polyethylene glycol could speed up the erosion [9]. However, the *in vivo* erosion rate may be affected by GI mobility. Due to the erosion controlled delivery, it is projected that the burst release effect can be minimized in the Egalet system.

On the other hand, the Egalet delivery system is easily fabricated for delayed release. Delayed release is gaining popularity for the enhancement of local effect or chronotherapy. The release of drug is delayed in a certain period of a time in GI tract and release in a bolus dose or a designated modified release. One area of delayed release applicable is to achieve colonic delivery for some therapeutic agents. On the other hand, the delayed release may provide advantages of a time release. The release of the drug can be timed to match the natural rhythms of a disease such as the morning stiffness and pain experienced by arthritis patients on waking.

A delayed release can be accomplished through three-compartment tablets including a coat, a drug release matrix, and a lag component. The lag component provides a predetermined delay for the drug release. After the lag component is eroded, the release drug is initiated in a designed mode as depicted in Figure 16.4.

Egalet delivery technology is developed based on standard plastic injection molding to ensure accuracy, reproducibility, and low production cost. It is being actively evaluated for development of numerous controlled release formulations by various companies.

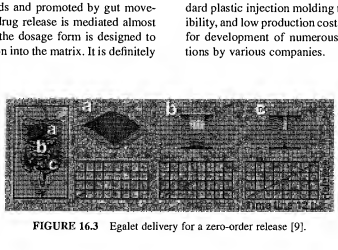

FIGURE 16.3 Egalet delivery for a zero-order release [9].

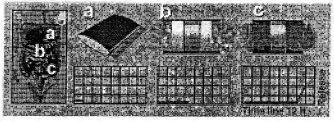

FIGURE 16.4 Egalet delivery for a delayed release [9].

16.3.3 Bioadhesive Oral Delivery

Bioadhesive delivery could be applied to oral controlled release. Bioadhesive polymers tend to adhere to the mucin/epithelial surface and find applications in buccal, ocular, nasal, and vaginal drug delivery. Those polymers could also help increase the residential time of solid dosage forms in the GI tract to improve gastroretentive delivery. On the other hand, bioadhesive polymers enable oral dosage forms stay close to epithelial layer and benefit the quick flux of drugs after dissolution. It could enhance oral absorption or improve localized therapy if the disease occurred in the GI tract.

Bioadhesion is an interesting phenomenon of the attachment of a synthetic or biological polymer to a biological tissue [10]. Adhesion could occur either with the epithelial cell layer or with the mucus layer. Adhesion to the mucus layer, namely, mucoadhesion, is more related for oral delivery. The GI tract is covered by a layer of mucus. Polymers containing hydrogen bonding groups tend to bind to the mucus layer. The mechanism of mucoadhesion is not fully understood. It is proposed that the attraction forces such as hydrogen bonding, van der Waals, and charges make polymers to have a close contact with the mucus. The close contact further promotes the penetration of polymers and formulation of entanglements with the mucin [10]. Many natural polymers and pharmaceutical ingredients show bioadhesive properties. Those polymers are carbomers, chitosan, starch, polymethacrylic acid, hydroxypropylcellulose, hydroxypropyl methylcellulose, and sodium carboxymethylcellulose. Bioadhesive polymers could be formulated with drugs in monolithic or multiparticulate forms to achieve controlled release.

Bioadhesive delivery could benefit the controlled release of drugs with narrow absorption window. Many drugs have a narrow absorption window from the proximal part of the GI tract due to transporter-mediated absorption. Increasing the residence time in the upper GI tract could extend and enhance the absorption. It has been reported that mucoadhesive microspheres of acyclovir made from ethylcellulose and Carbopol achieved a better bioavailability than a suspension formulation [11]. The mucoadhesive microspheres has an AUC_{0-t} of 6055.7 ng h/mL and a mean residence time of 7.2 h whereas the suspension has an AUC_{0-t} of 2335.6 ng h/mL and an MRT of 3.7 h. Combination of bioadhesive polymers with another mechanism possibly will improve the degree of success of gastroretention, which is very challenging to achieve. Chavanpatil et al. have discussed the development of a novel sustained release, swellable, and gastroretentive drug delivery system for ofloxacin with additional bioadhesive properties [12]. Varshosaz et al. have reported the design and *in vitro* test of a bioadhesive and floating drug delivery system of ciprofloxacin [13].

Bioadhesive delivery is advantageous in providing sustained release for localized therapy. Deshpande et al. have published a study about the design and evaluation of oral bioadhesive-controlled release formulations of miglitol, intended for the prolonged inhibition of intestinal α-glucosidases and the enhancement of plasma glucagon like peptide-1 levels [14]. Pectin-based microspheres for the colon-specific delivery of vancomycin have been developed by Bigucci et al. [15]. The microspheres made of pectin and chitosan show desirable mucoadhesive properties.

16.3.4 Computer Modeling

The biggest challenge for developing of controlled release products is *in vitro–in vivo* correlation. Fabricating a drug formulation with a zero-order release *in vitro* is less demanding than predicting the *in vivo* performance. The GI tract is much more complicated than a dissolution unit. Influences from pH, food, GI mobility, regional absorption, bile salts, and gut metabolism are too complex to formulate as several simple mathematical equations. Computer simulation software are useful tools for formulators to study the drug molecules and propose target release profiles. Softwares are also applicable for deconvoluting animal and human pharmacokinetic (PK) data and provide feedback for further formulation optimization.

Advanced software packages for modeling oral absorption are physiology-based simulation softwares including iDEA, GastroPlus, and SimCYP.

iDEA, a software for predicting oral drug absorption, has been developed according to a physiologically multiple-compartment model invented by Grass [16]. The Grass' model divides the GI tract to five compartments including

the stomach, duodenum, jejunum, ilcum, and colon. Oral adsorption of a drug is simulatcd on threc paramcters—solubility, permeability, and tissue surface area in all compartments. iDEA could use pcrmeability data from Caco-2 ccll and have thc capability to calculate solubility and permeability from a simplc structure input. iDEA is convenient to use for predicting oral absorption of ncw chemical entities in early discovery. Several successful cases have been published about using iDEA to predict oral absorption, including ganciclovir, kctorolac, naproxen, and atenolol [17]. However, iDEA does not consider important factors such as first-pass metabolism, transport process, dissolution, and prccipitation. It could not be used for evaluating formulations. iDEA is gradually phasing out while GastroPlus, a more sophisticated software, is gaining popularity.

GastroPlus is one of widely used software packages for modeling oral absorption of solid dosage forms. GastroPlus is an advanced software to simulate oral absorption, pharmacokinetics, and pharmacodynamics in animals and human based on molecular, physical, biopharmaceutical, and pharmacological attributes of a drug. The oral absorption module is based on an absorption model named advanced compartmental and transit model (ACAT) [18]. In GastroPlus, there are nine physiological compartments for human in line with diffcrent segments of the GI tract [19] (Table 16.2). A sct of differential equations are used to simulate the kinetics of drug release, precipitation, and absorption in the nine compartments. It takes into considcration pH-dependent solubility, gut, and liver metabolism, and regional absorption. GastroPlus is very useful in modeling the effect of solubility, particlc size, and dose on the extcnt of oral absorption for a specific drug (Table 16.3). GastroPlus also contains sophisticated pharmacokinetics (PK) simulations. The PK simulations could calculate PK parameters from intravenous and oral PK data, fit complex nonlinear metabolism and transport, and predict PK profiles based on PK parameters and kinetics of oral absorption. GastroPlus has been used as a tool in preclinical compound selection to assess absorption liability [20], cstablish *in vitro–in vivo* correlation (IVIVC) to justify biowaiver [21], and study food effect on pharmacokinetics [19].

There is a controlled release module in the software package. The oral absorption could be simulated with an input of *in vitro* controlled release profilc. The data input could be one of three ways, tabulated data with linear interpolation, tabulatcd data with cubic spline interpolation, or Weibull function parameters. The absorption–time profile and bioavailability can be simulated with various release rates and profiles. The impact of physicochemical properties such as pH-dependcnt solubility and physiological parameters can be inspccted at the same time. With the hclp of the PK module, animal and human intravenous (IV) and immediate release (IR) PK data could be dcconvoluted to help the simulation of controlled release formulations. Various controlled rclease formulations could bc studied in GastroPlus, including gastric retention, multiparticulatc, integral tablet, and enteric-coated tablet and capsule. A study by Lukacova et al. demonstrated that GastroPlus is very useful in modified release formulation developmcnt. GastroPlus has been applied to obtain simulated modcls for adinazolam and metoprolol about thc absorption, PK, and pharmacodynamics (PD) after IV and immediate release oral administration [19]. The fitted model for adinazolam was then utilized to study thc PD profile for a modified release (MR) formulation and to proposc a ncw formulation with desired onset and duration of action. The obtained metoprolol model is useful for understanding the *in vivo* profiles of MR formulations.

Similar to GastroPlus, SimCYP ADME simulator is a powerful platform for the prediction of drug absorption, PK, and drug–drug interaction [23]. The simulator consists of a huge database of human physiological, genetic, and epidemiological information. By incorporating *in vitro* data, it simulates a virtual clinical trial to predict pharmacokinetic profilcs in a "rcal-world" population. The advanced dissolution, absorption, and metabolism (ADAM) modcl in thc SimCYP simulator is a compartmental transit model having

TABLE 16.2 Nine Compartments and Physiological Parameter for a Fasting Adult Human (85 kg) Proposed in GastroPlus [19]

Compartment	Volume (mL)	Transit Time (h)	pH
Stomach	50	0.25	1.3
Duodenum	48	0.26	6.0
Jejunum 1	175	0.95	6.2
Jejunum 2	140	0.76	6.4
Ileum 1	109	0.59	6.6
Ileum 2	79	0.43	6.9
Ileum 3	56	0.31	7.4
Cecum	53	4.50	6.4
Ascending colon	57	13.5	6.8

TABLE 16.3 Input Variables for GastroPlus [22]

Parameter	Input
Chemical structure	ISIS structure
Dose information	Dose strength, subsequent dose, dose interval, dose volume, drug particle density, effect particle radius, dose form
Solubility	Solubility at different pH (1.5–7.5)
Permeability	CaCO2 permeability or calculate Peff
Molecular properties	pK_a, log *P*, log *D*

seven compartments for the small intestine. It takes into account of physiological variables such as gastric emptying time, small intestinal transit time, the radius, and length of the small intestine. It considers the dynamics of drug dissolution, precipitation, degradation, intestinal metabolism, and active transport. It calculates the effect of bile salts on dissolution and the effects of pH and transporter on permeability. It was reported that the plasma concentration profiles for three modified release formulations (fast, moderate, and slow) of metoprolol have be successfully predicted [24].

It is clear that both GastroPlus and SimCYP will play a more important role in future controlled release formulation development.

16.4 ORAL DELIVERY OF BIOPHARMACEUTICALS

Development of biopharmaceutical agents is thriving for past two decades owing to many breakthroughs in genomics and biotechnology. Hormones, growth factors, and cytokines are important therapeutic agents for managing and curing many diseases including diabetes, anemia, and hepatitis. Monoclonal antibodies with specific molecular targets are blockbuster drugs for cancer and rheumatoid arthritis. Many new vaccines have been developed to cope with some challenging infection diseases such as HIV, HCV, and HBV. Oligonucleotides such as small interferon RNA appear to be very promising as specific therapeutic agents for many unmet medical needs.

16.4.1 Challenges in Oral Delivery of Biopharmaceuticals

Though many bioactive molecules have either become successful commercial products or reached clinical trials, most of them are delivered by intravenous or subcutaneous injection. The development of noninvasive administration of peptide drugs especially through oral delivery route still remains not only a great challenge but also an exciting mission.

Oral delivery of biopharmaceuticals is challenged by instability in gastrointestinal fluids and poor permeability. First, biopharmaceuticals have poor stability in the GI tract [25–27]. Proteins and nucleotides would be denatured at acidic pH in the stomach, which results in the loss of biological activities. Proteases and nucleases in GI fluids also degrade biopharmaceuticals. Pepsin in the stomach and proteases secreted from the pancreas cleave peptide bonds and break down active therapeutic proteins and peptides. Moreover, proteins and nucleotides have poor intestinal permeability and are difficult to get absorbed due to their large molecular weight and hydrophilic nature [28, 29]. It has been reported that the mucus layer in the intestinal lumen tends to bind charged molecules such as proteins and nucleotides, which also prevent oral absorption [30, 31].

16.4.2 Approaches in Overcoming Challenges in Oral Delivery of Biopharmaceuticals

Progress has been made for oral delivery of peptides or small proteins because of their relative small molecular weight [32–34]. Several approaches are being taken to improve the GI stability and enhance absorption, like enteric coating, protease inhibitors, and permeation enhancers.

Enteric coating of oral dosage forms has been utilized to avoid the release of therapeutic agents in the stomach, which mitigate the denaturc caused by acidic pH and the degradation catalyzed by pepsin. Enteric polymers like Eudragit S100 can ensure that oral dosage forms such as tablets, capsules, or pellets pass through the stomach without release and deliver therapeutic peptides to the small intestine or the colon [32]. Moreover, specific colonic delivery has been proposed to be advantageous to the oral delivery of peptides or proteins due to their lower proteolysis activity and greater responsiveness to absorption enhancers [33].

On the other hand, the enzymatic cleavage by pancreatic proteases in the intestine might be reduced by the inclusion of protease inhibitors in formulations. Protease inhibitors applicable are either specific enzyme inhibitors such as aprotin or trypsin inhibitors originated from animals or plants [34–36]. It has been reported that organic acids are also effective in inhibiting pancreatic proteases through controlling local pH, which are more active in neutral and alkaline pH than acidic pH [37].

In addition, permeation enhancers are needed to reduce the barrier for the oral absorption of peptides. Many permeation enhancers are surfactants or detergents such as sodium cholate, fatty acids, bile salts, and phospholipids [38–40]. Aside from solubilizing poorly soluble peptides, absorption enhancers wield their effects by increasing the permeability of biological membrane and fluidizing the lipid membrane. Consequently, the tight junction between mucosal cells are loosened and become more permeable to peptides. Calcium chelating agents enhance the permeation by disrupting the tight junction [41]. Another efficient agent to loosen tight junction is zonula occludens toxin or Zot [42–44]. Zot is a single polypeptide chain of 399 amino acids present in toxigenic strains of *V. cholera*. It has the ability to reversibly alter intestinal epithelial tight junction, which allows the passage of macromolecules through mucosal barriers. An encouraging 10-fold increase in insulin absorption has been observed in both rabbit jejunum and ileum *in vivo* with Zot [44]. However, there is a concern that the loosening of tight junction may have long-term toxic effects and pose undesirable consequences for the absorption of other drugs, nutrients, or pathogens. Another strategy to improve absorption of peptide is to use bioadhesive

TABLE 16.4 Ingredients Used for Oral Delivery of Peptides

Ingredients	Function	Examples
Enteric coating polymer	Prevention of degradation in the stomach; targeted delivery to the colon	Eudragit L30D-55, Eudragit FS30D
Protease inhibitor	Inhibition of pancreatic enzymes	Aprotin, trypsin inhibitor, chymotrypsin inhibitor, Bowman-Birk inhibitor, organic acids
Permeability enhancer	Decrease of the interaction with mucus layer; improvement of paracellular and transcellular permeability	Acylcarnitine, salicylates, sodium cholate, long-chain fatty acids, bile salts, surfactants

polymers. Bioadhesive polymers could increase the residence time and provide a prolonged delivery. Moreover, bioadhesive carriers localize the associated drugs to absorption sites, which also promotes oral adsorption [45].

It is possible that combination of above strategies could result in the improvement of bioavailability for therapeutic peptides (Table 16.4).

16.4.3 Several Oral Delivery Systems for Biopharmaceuticals

Unigene (Fairfield, NJ) has developed a proprietary technology to deliver various therapeutic peptides orally [46]. The formulation is an enteric-coated capsule or tablet with organic acids and permeability enhancers mixed with a peptide (Figure 16.5).

It has been claimed that the oral delivery system by Unigene could achieve 1–10% bioavailability for various peptides and small proteins, depending on size, charge, and structure [46]. Capsules and tablets of salmon calcitonin, a 32-amino acid peptide for the treatment of postmenopausal osteoporosis, have been studied in rats, dogs, and humans. Calcitonin is a polypeptide hormone that regulates the calcium and phosphorous metabolism. A significant amount of intact salmon calcitonin has been detected after oral dosing in rats, dogs, and humans [46]. The C_{max} (250–3500 pg/mL) in dog and human was linear with dose from 0.33 to 4.58 mg of salmon calcitonin. The phase I study in human has demonstrated that an oral dose of 0.5 mg was able to achieve a mean C_{max} of 300 pg/mL with T_{max} ranging from 90 to 180 min. Unigene has entered a phase II clinical trial for oral salmon calcitonin. Oral formulations of therapeutic peptides, such as human parathyroid hormone, glucagon-like peptide-1, and leuprolide, are being developed using the same platform and are in preclinical or early clinical test.

FIGURE 16.5 Oral delivery system developed by Unigene [46].

There are remarkable interests in developing oral formulation for insulin. The progress of oral delivery of insulin has gained significant media attention. Oral delivery of insulin has been demonstrated in diabetic dog using enteric-coated microcapsule with sodium cholate as an absorption enhancer and the soybean trypsin inhibitor as a blocker to proteolysis degradation [47]. A clinical study of oral insulin by Emisphere did not generate promising results for further development, revealing the significant hurdle for oral delivery of therapeutic peptides and protein. Nanoparticle formulation is gaining attention right now, which may be able to enhance the overall bioavailability of oral doses of proteins and peptides [48].

It is clear that the route to reach approval and market for oral delivery of peptide is still formidable. Tremendous effort in research and development is being made due to the significant benefit of oral dosage form regarding patient compliance and acceptance. Besides formulation approach, chemical modifications have been utilized to improve the stability or absorption of peptides [49, 50].

Complexation hydrogel has been reported to be a promising carrier for the intestinal delivery of peptides such as interferon beta and calcitonin [51]. Therapeutic peptides could form complex with hydrogels such as poly(methacrylic acid) grafted with poly(ethylene glycol). The hydrogels have multiple functions to ensure the stability of peptide. Peptides are protected in the acidic environment in the stomach because the hydrogels do not swell in acidic conditions. The hydrogels are designed to swell in neutral or alkaline pH to release the peptides in the intestinal lumen. In addition, the advantages of those hydrogels are their mucoadhesive characteristic to enhance adsorption and potentials to inhibit proteolysis degradation by chelating calcium. It was demonstrated that the absorption of interferon beta and calcitonin has been significantly improved through complexing with hydrogels compared with a solution formulation. The area

TABLE 16.5 AUC Values Following *In Situ* Administration of Interferon β-Loaded P(MAA-*g*-EG) Microparticles into the Ileal Segments [51]

Dose ($\times 10^6$ IU/kg)	AUC	
	Interferon β Solution	Interferon β-loaded P(MAA-*g*-EG)
0.75	6.7 ± 6.0	48.4 ± 6.7^b
2.0	74.6 ± 14.2	154.4 ± 29.0
6.0	84.8 ± 32.1	257.9 ± 80.7

AUC: area under the curve.

Each value represents the mean ± S.E. from $n = 3$–8.

"$p < 0.05$, significant difference among doses of "interferon β solution" or "interferon β-loaded P(MAA-*g*-EG)."

$^b p < 0.01$, significant difference compared with the corresponding "interferon β solution."

under the curve (AUC) of hydrogel formulation was 2–6-fold higher than the solution formulation after being delivered specifically to the jejunum area. It is clear that this approach is a significant breakthrough to pursue oral delivery of peptides (Table 16.5).

16.4.4 Oral Delivery for Vaccines

Vaccination is a long established therapy against various infectious diseases caused by bacteria and viruses. Vaccine is a biopharmaceutical preparation that establishes or strengthens the immunity of animals or humans to a particular infectious disease. There are many types of vaccines available, which include killed microorganisms, live and attenuated microorganisms, inactive toxoids, protein subunits, polysaccharide–protein conjugates, and DNA vaccines. The immunization of vaccines is mainly relied on parental route. However, there are substantial interests in developing oral vaccines for humans and animals due to their more desirable acceptance, avoidance of needles, easy administration, and low cost.

Challenges are expected to be encountered for the oral immunotherapy of vaccines, such as instability and poor absorption in gastrointestinal tract. Various ingredients have been explored to improve oral bioavailability, which include hexose monosaccharide, ethyl alcohol and water vehicles, oxygen-containing metal salts, enteric coating, and poly(lactic-*co*-glycolic) acid microspheres [52]. It has been reported that lipid formulations were capable of enhancing the oral vaccination in animal studies [53]. In a study reported by Vipond et al., the oral vaccination of Bacille Calmette–Guérin (BCG) against tuberculosis has showed promising results in animal studies [53]. Lipid formulations containing BCG strains induced significant γ-interferon response in mice and provided proved protection against TB aerosol challenge in guinea pigs. The effectiveness of vaccination of lipid formulation was superior to unformulated BCG and equivalent to subcutaneous immunization. Nayak et al. have studied the formulation of rotavirus with polylactide (PLA) and polylactide-*co*-glycolide (PLGA) for vaccination [54]. Rotavirus is a virus that causes severe diarrhea, mostly in babies and young children. Rotavirus vaccine is an oral vaccine delivered as a solution. In this study, rotavirus was trapped in PLA and PLGA to form microparticles, which offered enhanced stability in the stomach and a sustained exposure. A single-dose oral immunization with 20 mg of antigen entrapped in PLA and PLGA particles has exhibited improved and long-lasting immunization than the soluble antigen.

16.4.5 Oral Delivery for Nucleotides

In contrast to protein-based drugs, nucleotide-based therapeutics have not attained major breakthroughs of reaching patients despite several decades of effort in research and development. Biopharmaceuticals based on antisense RNA showed early promises in animal studies but were barely able to demonstrate reliable and sufficient efficacy data in clinical trials. The main hurdle is effective delivery. Nucleotide-based drugs have to enter inside cells to be effective whereas many protein therapeutics act on receptors on cell surfaces. In recent years, development of nucleotide-based biopharmaceuticals, specific on RNA interference (RNAi), has gained new waves of interest. Major pharmaceutical companies such as Merck, Novartis, and Pfizer are rushing internal resources and external investment to develop RNAi therapeutics.

RNAi is a RNA-dependent gene silencing process in life cells found in eukaryotes including animals [55]. RNAi is an important cell defence against parasitic genes such as viruses and transposons. On the other hand, RNAi also directs gene expression and regulates development of eukaryotes. Small interference RNA (SiRNA), a class of 20–25 nucleotide-long double-stranded RNA molecules is central to RNA interference. The siRNA has been successfully used for genomic studies and drug target validation recently. It is anticipated that siRNA based on therapeutics will play a significant role in fighting against infectious diseases such as HIV, HCV, and HBV in the future. By the way, progression of many diseases such as cancers, Alzheimer's diseases, and diabetes is related to the activity of multiple genes. It is expected that turning off of a gene with a siRNA may provide a therapeutic effect to cure or modulating various diseases. The siRNA has the potential to become next generation of new therapies for many unmet medical needs with even greater impact than the introduction of monoclonal antibodies.

Some promising results have been obtained in cell-based *in vitro* models and *in vivo* animal models through localized delivery. A study carried out by Crowe has demonstrated that siRNAs targeted for HIV chemokine receptors, CXCR4, and CCR5, are effective in blocking the entry of HIV virus

in vitro [56]. The silencing of hepatitis A and hepatitis B, influenza, and measles genes using siRNA is being actively pursued for potential therapy [57–59]. However, effective systemic administration of siRNA for therapeutic use faces mammoth challenges such as poor stability and limited cellular uptake. siRNAs could not freely pass cell membrane due to its strong anionic charge of its backbone and large molecular weight (about 13 kDa). On the other hand, unmodified, naked siRNAs have poor stability in blood and serum, as they are rapidly degraded by endo- and exonucleases.

Chemical modifications in the backbone, base, or sugar have been engaged to enhance stability without adversely affecting gene silencing activity [60]. Delivery through viral vectors has been reported to be successful in many cases of animal studies. There are some safety concerns about the clinical use, such as potential mutagenicity or oncogenesis. Development of nonviral delivery system has been actively advanced including chemical modification, linking to cell penetrating peptide, and lipid-based delivery [60]. A major breakthrough of nonviral delivery is to utilize antibodies to direct the delivery of siRNA. Liposomes or protein complexes carried with siRNA can be coated with antibodies. Antibodies will trigger the cell membrane internalization after binding specific cell surface receptors to achieve the delivery of siRNA. It has been published that HER-2 siRNA could be delivered to tumor cells both *in vitro* and *in vivo* with liposome coated with antitransferrin scFv [57]. Kumar et al. have demonstrated that a complex with antiviral siRNA and a CD7-specific single-chain antibody conjugated to oligo-9-arginine peptide was able to achieve significant anti-HIV activity in an HIV-infected mice model [58].

Many ongoing trials with siRNA mainly relied on localized delivery or parental route. Oral delivery of siRNA is clear to face even bigger hurdle. It is optimistic that the technologies under development for oral delivery of proteins and knowledge gained for siRNA will promote a new generation of formulation scientists to innovate and bring this very promising category of drugs to patients.

16.5 NEW PLATFORM TECHNOLOGIES FOR ORAL CONTROLLED RELEASE

As discussed above, oral controlled release has been advanced to new frontiers such as controlled delivery of poorly soluble compounds and biopharmaceutical oral formulation. Moreover, new technologies and novel processes are being innovated to achieve lower cost, higher efficiency, more robustness, and better quality. These new technologies include hot melt extrusion (HME), injection molding, printing techniques, and dry coating. It is obvious that these new technologies will have a huge impact on formulation development of sustained release, modified release, and targeted release oral delivery systems.

16.5.1 Hot Melt Extrusion for Controlled Release

Hot melt extrusion (HME) is a widely used process in plastic, rubber, and food industry. In recent decades, HME is emerging as a powerful process technology for drug delivery, HME is applicable to the manufacture of different variety of solid dosage forms including granules, pellets, tablets, rods, and films for oral, transdermal, and implant delivery. Oral dosage forms from HME can be immediate or controlled released. The primary application is to make solid dispersion formulations to enhance solubility for poorly soluble compounds. However, its value in developing controlled release formulations has gained extensive attention.

There are many advantages of HME for controlled release formulation (Table 16.6). HME process is solvent free and anhydrous, which is more environment friendly and is more desirable for drugs with physical and chemical stability sensitive to water. It only involves few stages in a single continuous unit operation that simplifies process development and scale-up. Very high load could be achieved through HME. Due to the intensive mixing and agitation during the process, drug particles are uniformly suspended or melted in a polymer matrix to achieve superior content uniformity. Many kinds of dose forms such as tablets, pellets, rods, and films and different geometries can be produced by HME. For drugs with poor solubility, amorphous form can be generated to achieve sufficient solubility for controlled release. However, HME does demand drug molecules to have acceptable thermal stability to withstand the thermal process. Many commercial products have been successfully launched via HME process, such as Kaletra (lopinavir/ritonavir/copovidone) tablets, Certican tablets (everolimus/HPMC), Rezulin tablets (troglitazone/PVP), and Sporanox capsules (itraconazole/HPMC).

TABLE 16.6 Advantages and Disadvantages of HME

Advantages	Disadvantages
• Continuous process • Few unit operations • Solvent free and anhydrous process • High drug load • Better content uniformity • Formation of amorphous • Variety of dosage forms such as tablets, pellets, implants, films • Wide range of geometry	• Thermal process (drug/polymer stability) • Flow properties of polymer are essential • Limited number of polymer • High density and low compressibility

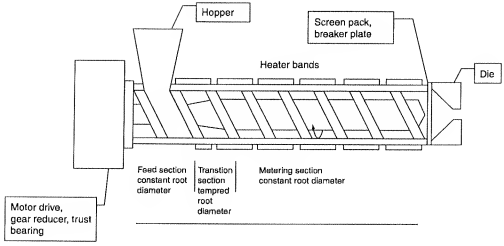

FIGURE 16.6 Component parts of single-screw extruder [61].

HME is a single-unit operation with four stages:

1. melting/softening of drug/polymer mix in a heated chamber;
2. mass transport of melted or softened drug/polymer mix through the barrel using a screw system;
3. extrusion of the drug/polymer mixture through a die;
4. cooling and fabricating the mixture to a designed shape.

The structure of a typical single-screw extruder is shown in Figure 16.6 [61].

Formulation development of a controlled release formulation using HME involves selection of polymers, plasticizers, and releasing modulators that are compatible with a targeted drug. The drug release rate is modified through the optimization of drug load, type and level of polymers, amount of plasticizers, and quantity of releasing modulators. Polymers used for melt extrusion need to have good thermal stability. Some commonly used polymers for controlled release, such as hydroxypropyl methylcellulose, ethylcellulose, polyethylene oxide (PEO), are suitable for HME formulation (Table 16.7). Plasticizers are commonly included to HME formulations to lower the glass transition temperature and reduce the viscosity of melt mixture. The presence of plasticizers increases the flexibility of the extrudate and enables the process to take place in a much lower temperature. Lower process temperature helps mitigate the degradation problems. On the other hand, amount of plasticizers could influence the drug release rate. The drug release rate could also be modified by the addition of releasing modulators such as lactose, povidone, or low molecular HPMC. Process optimization for HME involves the study of process temperature, holding time, and feeding rate.

Formulation development of a controlled release system using HME is a combination of science and art. The design space for a target dissolution profile is substantially broad for formulation scientists to explore, which includes the selection and optimization of drug load, carrier polymer, plasticizer, and releasing agent. In certain circumstances, combination of two polymer carriers will help to develop a formulation with a custom dissolution profile. Coppens et al. have demonstrated that a HME formulation of acetaminophen (APAP) could be prepared using both hypromellose (HPMC) and polyethylene oxide to attain different mode of

TABLE 16.7 Polymer Carriers Applicable for Controlled Release Formulation via HME Process

Polymer	Trade Name	Physical Properties
Polyethylene oxide	Polyox WSR	Highly crystalline powder, hydrophilic, melting point 70°C, glass transition -40 to -60°C, thermal stability up to 350°C
Hydroxypropyl methylcellulose	Methocel	Hydrophilic, glass transition 160–210°C, thermal stability up to 250°C
Hydroxypropylcellulose	Klucel	Hydrophilic, thermal stability up to 260°C, glass transition 130°C
Ethylcellulose	Ethocel, Aqualon EC	Hydrophobic, amorphous glass transition 129–133°C, crystalline melting point 180°C, thermal stability up to 250°C

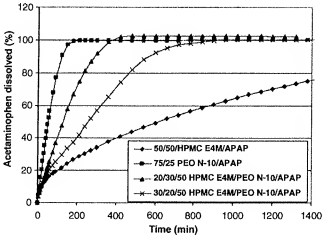

FIGURE 16.7 HME formulations of acetaminophen [62].

release profiles [62]. As shown in Figure 16.7, combination of HPMC and PEO helps the development of formulations with a 6–10 h sustained delivery with a complete release, which is more versatile for further modification than single polymer carrier.

A more efficient way to adjust release profiles is to select a suitable plasticizer or release modifier and vary its amount.

The most striking feature of HME process is its ability to prepare a controlled release formulation for poorly soluble compounds. Molecular dispersion could be prepared to enhance the solubility at the same time the release rate is customized to achieve immediate release, modified release, or sustained release depending on the targeted profile. It has been demonstrated in a case study by Zhu et al. that solubilization and controlled release can be accomplished at same time [63]. Tablets of indomethacin, a poorly soluble drug, were prepared by HME with Eudragit RD 100, a copolymer of acrylate, and methacrylate. It has been found that indomethacin formed a solid solution with Eudragit RD 100 and the release of indomethacin was controlled by the matrix of Eudragit RD 100. The inclusion of Pluronic® F68, Eudragit® L100, or Eudragit® S100 in the HME formulations facilitated the release rate [63].

16.5.2 Injection Molding for Controlled Release

Like hot melt extrusion, injection molding (IM) is a thermal process widely used in plastic industry. A polymer or a polymer mixture is melted and injected to a mold to form a finished product. Injection molding shares some common features with melt extrusion, such as the mass transport of polymer using a screw and the melting process. However, HME is more tailored for production of bulk products such as sheets, rods, and tubes. IM is designed to manufacture finished products in a single step, including bottles, caps, discs, or any designed articles. As shown in Figure 16.8, polymer resin is supplied to a machine through a hopper. After entrance into the barrel, the resin is heated to a proper melting temperature. The melted resin is injected into a mold by a reciprocating screw or a ram injector. The mold is cooled constantly to a temperature that lets the resin to solidify.

IM has been utilized for producing numerous medical designs in plastic parts, such as drug implants, delivery systems, and product containers. For example, polymeric microneedle for transdermal delivery can be fabricated using microinjection molding techniques [64].

FIGURE 16.8 Drawing of a basic injection molding.

Similar to melt extrusion, IM can be applied in developing controlled release formulations to achieve sustained release, modified release, or delayed release. A major advantage of IM is that finish products are produced in a single step, whereas materials from melt extrusion may need further formulation effort to become a dosage form. A study has been reported by Quinten et al. about developing sustained release matrix tablets of metoprolol tartrate using IM. Matrix tablets of metoprolol were formulated with ethylcellulose as the matrix polymer, dibutyl sebacate as the plasticizer, and hypromellose as the release modifier. It has been found that metoprolol tartrate existed as a solid dispersion in the matrix tablets prepared by IM. Combination of 50% hypromellose with ethylcellulose resulted in a complete and first-order drug release profile with drug release controlled via the combination of diffusion and swelling/erosion [65].

Moreover, IM is more sophisticated than HME in the manufacture process so that it could be used for design and production of more complicated delivery system. It is projected that IM will advance significantly due to its ability to fabricate complex delivery system. The prominent case of IM for controlled release is the invention of Eaglet delivery system, an erosion-based delivery system feasible for prolonged release and delayed release, described in the previous section.

16.5.3 Printing Techniques for Controlled Release

While melt extrusion has become a practical approach for controlled release and IM is advancing the frontier, printing techniques for controlled release is more a technology for tomorrow. It is a fabulous platform but it may take long way to be applicable for market products.

Inkjet printer is a cheap and common consumer goods. However, the process of printing using inkjet is a complicated technical process. The printing process engages the rapid creation and release of liquid droplets through hundreds of delivery nozzles with a predetermined mode. The deposition position on a substrate is precisely controlled and can be preprogrammed.

It is very interesting to apply such a sophisticated technology to fabricate delivery systems. Delivery systems can be precisely designed and manufactured in three dimensions. The concept of printing itself can be prototyped to be a novel delivery system. Based on its own inkjet technology, Hewlett-Packard is developing a smart patch for transdermal delivery [66]. The patch consists of numerous microneedles linked to respective drug reservoirs. Four hundred cylindrical reservoirs, each one attached to its own microneedle, can be present in one in.^{2} of the patch. Drug administration is governed by an embedded microchip and powered by a low-power battery. This novel transdermal delivery system is applicable to numerous drugs that are not feasible for traditional delivery. It also has the flexibility to deliver various drugs and the potential to program according to biological signals.

It has been reported that printing technology can be utilized to fabricate artificial bones. The shape was designed based on the image data of bone deformity. And internal structure was built layer by layer through printing a water-based polymer adhesive onto thin layers of powdered α-tri-calcium phosphate (TCP). The polymer hardened the TCP. An artificial bone has been reproduced precisely through repeating powder laying and polymer printing [67].

Inkjet printing also offers significant advantages for the coating of small medical devices including coronary artery stents [68]. Coronary artery stents coated with a variety of pharmacological agents such as sirolimus and paclitaxel are used to prevent restenosis. Traditional processes for the manufacture of drug-coated stents are dipping, ultrasonic spray coating, airbrush painting, and deposition along the struts using syringes. These processes lack tight manufacture control, retain high variability in drug concentration, and challenge the delivery in a more controlled manner. It is clear that inkjet printing is going to transform this field due to its preciseness and sophistication. The drug and polymer solutions can be put very precisely in both location and amount onto a stent. Drug gradient is flexible to engineer and thickness of polymer at different location is feasible to fabricate to gain desirable release kinetics. Coating could be very complicated, including multiple layers of polymers or several drugs. Moreover, the development process is more efficient than traditional processes. Drug waste is much less.

Inkjet printing also finds its edge in biomedical fields such as targeted gene delivery [69], tissue engineering [70–72], and the development of biodegradable implants [73].

Application of inkjet printing in controlled oral delivery has been advanced steadily since the invention of three-dimensional printing techniques by MIT in 1990s. Three-dimensional printing is a novel prototype technique with wide applications in the rapid and flexible production of prototype parts, end-use parts, and tools directly from a CAD model [74]. It has exceptional flexibility in building parts with complicated internal and external geometry and unprecedented control of location, material composition, microstructure, and surface texture, using various materials including ceramics, metals, polymers, and composites.

The process of three-dimensional printing is illustrated in Figure 16.9. A three-dimensional product is built layer by layer by powder delivery and printing of binder solution. Each run starts with a thin layer of powder delivered over the surface of a powder bed. A binder material is sprayed by inkjet head to join particles at defined positions based on design from CAD. The powder bed supported by a piston is lowered to allow next layer to be printed. This layer-by-layer process recurs until the product is finished. Following

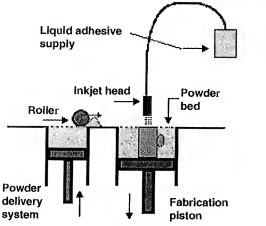

FIGURE 16.9 Diagram of three-dimensional printing [74].

a thermal treatment or other curing methods, loose powder is removed, leaving the fabricated product.

It is obvious that three-dimensional printing is applicable to developing sophisticated oral controlled release formulations due to its superior spatial and composition control. It has been reported that tablets with zero-order release characteristics could be attained through manipulating drug gradient, polymer gradient, geometry, and internal structure using three-dimensional printing [75]. Yu et al. have found out that a gradient distribution of release retardant polymer is functional in developing an erosion-based tablet with zero-order release [75]. The tablet consisted of a sandwiched structure with top and bottom layers impermeable to water penetration and drug diffusion. The drug release was controlled by the rate of erosion in the middle layer. A near-linear erosion rate has been achieved through printing release retardant polymers such as ethylcellulose in a decrease gradient from the periphery to the center. Another approach is to increase the drug concentration along the central axis to fulfill zero-order kinetics. It is clear that only printing techniques could deliver such precise concentration and texture control. It does provide another alternative to formulate zero-order release if not superior to traditional technologies.

Printing technology is also applicable in developing delayed release formulations such as time release or site-specific release. Current approaches for such formulations mainly rely on coating processes that involve multiple polymers or several layers of coating. The batch process approach is difficult to ensure the consistent coating of different single units. It is obvious that the performance of those dosage forms is variable and may lack reproducibility. It could be foreseen that printing technology is capable of advancing this field greatly due to its ability to be preprogrammed and to be precisely controlled to fabricate a sophisticated delivery system. Thickness of delayed layer, amount of permeability enhancer, geometry, and locations of drugs can be easily engineered and precisely controlled. Katstra et al. have developed a pulsatory tablet of sodium diclofenac with two pulses of release using three-dimensional printing technology [76]. Sodium diclofenac was printed to two separate areas in a continuous enteric excipients phase in the tablet. Three-dimensional printing has endless flexibility to accommodate many ways of design and substantial engineering capability. It could be used for delivering multiple drugs in various modes. However, significant effort is needed to make this technology feasible for commercial manufacture.

16.5.4 Dry Coating

Coating is one of the major technologies to develop controlled release formulations including sustained release, modified release, and delayed release oral dosage forms. Coating is applicable to powder, granules, pellets, minitablets, tablets, and capsules to achieve desirable delivery profiles. Pan coating and fluid bed coating using solvent or latex are well established for many decades. For liquid coating, polymers, pigments, and excipients are mixed in an organic solvent or water to form a solution or dispersion. The coating solution or dispersion is sprayed into solid dosage forms in a pan coater or a fluid bed dryer and dried by hot air. Liquid coating has the disadvantages of significant solvent consumption, long process, and considerable energy use. On the other hand, there is a considerable challenge to develop very thick coating using liquid coating for delayed release or erosion-based controlled delivery. Dry coating, which is more environment friendly, is perceived to have the potential to eliminate some of the drawbacks of wet coating.

Two approaches could be used for dry coating, which are powder coating and compression coating. Powder coating is stemmed from metal coating. Powder materials are directly applied to a solid surface. Polymer particles are adhesive to the surface physically by electrostatic forces. The formation of coating is finished through a curing step by heat. Compression coating is more an extension of tableting technology. Coating material is compressed to surround an inner tablet through a multistep tableting process. Both techniques will be discussed in more detail in following paragraphs.

Powder coating is attained by applying fine particles to solid dosage forms and forming film by heat. Thermoplastic polymers are used for pharmaceutical coating. Plasticizers are often included to reduce the glass transition temperature, which allows the formation of film at a reduced temperature and with an improved flexibility. Depending on the way to promote the adhesion of particles onto the surface, powder coating is classified as plasticizer-dry-coating, electrostatic-dry-coating, heat-dry-coating, and plasticizer-electrostatic-heat-dry-coating.

For plasticizer-dry-coating, powder and a liquid plasticizer are sprayed using separate nozzles onto the dosage surface at the same time. The dosage surface and powder

particles are wetted with the plasticizer to promote the adhesion between them. A continuous film is formed after curing above the glass transition temperature of the polymer for a predetermined time. Heat curing helps the particle deformation and coalescing to form a film. It has been reported that the spraying of a small amount of water or hypromellose solution during curing was beneficial to the film quality of hypromellose succinate acetate-coated spheres and tablets [77]. Dry powder coating can be accomplished in a centrifugal granulator, a fluid bed dryer, or a pan coater. As illustrated in Figure 16.10, powder mixture is carried by a stream of compressed air and sprayed onto tablets while a plasticizer solution is sprayed at the same time. It has been demonstrated that powder coating was able to achieve similar coating efficiency and performance to liquid coating for spheres and tablets with the enteric coating polymer, hypromellose succinate acetate [77].

Another way to promote the adhesion of particles to solid dosage is to use heat. The technique is called heat-dry-coating, which was invented by Cerea et al. [78]. Coating is performed in a spheronizer. Polymer particles are continuously spread onto tablets while heated by an infrared lamp to promote the binding and film forming. However, this technique is only applicable to polymers with low glass transition temperature, such as Eudragit E PO, a copolymer of dimethylaminoethyl methacrylate and methacrylate. For a polymer with high glass transition temperature, a preplasticization with plasticizer is needed. Both plasticizer-dry-coating and heat-dry-coating have difficulties in preparing uniform and smooth coating with controllable coating thickness.

However, electrostatic-dry-coating is capable of achieving uniform coating with controlled coating thickness. Electrostatic coating is widely applied in coating of metal surface. Dry powder is propelled by compressed air and forced through a spray gun. During the process, particles become electrically charged and tend to adhere to metal surfaces via electrostatic binding. However, it is not straightforward to do electrostatic-dry-coating for pharmaceutical dosage forms due to the weak electrical conductivity. One of the approaches to improve electrostatic-dry-coating is to ground the tablet more effectively and direct charged particles onto the tablet surface more specifically through a unique instrument design. Based on its proprietary instrumentation of electrostatic-dry-coating, Phoqus Co. has developed Chronocort, a once-daily modified release formulation for the treatment of adrenal insufficiency. In another report, the electrostatic coating has been accomplished through an electrically grounded pan coater [79]. Coating materials with plasticizer were sprayed to tablets by an electrostatic spray gun for a predetermined length to achieve certain thickness of coating. The curing step by heat helped the formation of continuous and uniform coating.

Powder coating is an improved coating technique, which utilizes equipments similar to liquid coating. On the other hand, compression coating is just a compaction technique. Coating material is directly compressed to surround a core by tablet compression. The main advantage of compression coating is its capability to allow much greater weight gain than liquid coating or powder coating. This aspect makes it very desirable to develop time-based release formulations for targeted delivery or chronotherapy. Targeted delivery is to delay the release of a dosage form until reaching a specific gastrointestinal location such as the colon to treat localized diseases. Chronotherapy is to deliver drugs to match the circadian rhythm of some diseases such as asthma, arthritis, epilepsy, migraine, and allergic rhinitis. Drugs will be released after a preprogrammed lag time. Tablet formulations for time-based delivery are typically made of a rapid release core tablet covered by a barrier layer to delay the release.

It has been demonstrated in numerous studies that compression coating is an exceptional choice for developing time release delivery. Ghimirea et al. have developed a time release tablet of theophylline using compression coating [80]. A barrier layer consisting of glycerol behenate and low-substituted hydroxypropylcellulose was pressed around an immediate release core of theophylline. The coated tablets showed pulsatile release with a lag time dependent on the

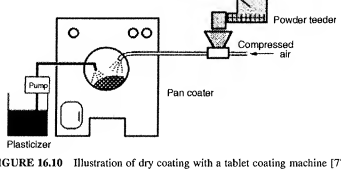

FIGURE 16.10 Illustration of dry coating with a tablet coating machine [77].

relative amount of glycerol behenate and low-substituted hydroxypropylcellulose. A tablet formulation of mesalamine has been developed by coating with layers of hypromellose Methocel E15 and Eudragit S100 to achieve a site-specific colonic delivery [81]. Lin et al. have reported that the lag time could be modulated from 1 to 16 h by modifying the type and amount of excipients of outer layer for a compressed coated tablet of sodium diclofenac [82].

Those cases were performed in lab scale and tablets were manufactured by manual processes. To achieve a reliable production, sophisticated instrumentation is needed to ensure the reproducible central position of core tablet, uniform thickness of coating layer, and consistent porosity of coating layer. One-step dry coating (OSDrC) technology invented by SKK in Japan is greatly advancing the possibility of manufacturing dry coating products in production scale.

OSDrC is accomplished through a uniquely designed rotary tableting machine [83]. This machine has a variable double punch configuration to support single-step production of dry-coated tablets. The position of core tablets is precisely controlled and the coating layer is very flexible for fabrication in geometry and thickness.

The tableting process is depicted in Figure 16.11. The rotary-type tableting machine uses only a single set of punches and dies. All punches have a double structure consisting of a center punch and an outer punch. The manufacture process involves three compressions. At the first compression, the lower-outer layer is formed. The core is compressed with the lower layer at the second compression.

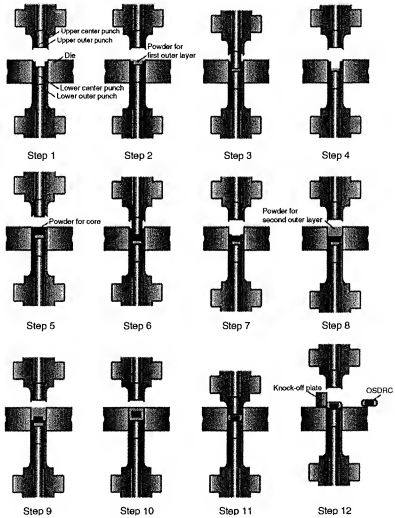

FIGURE 16.11 Procedure of OSDrC manufacturing process [83].

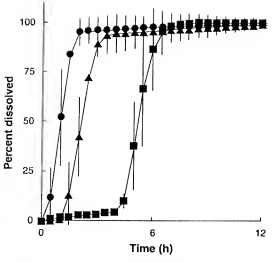

FIGURE 16.12 Effect of the outer layer thickness on the release of acetaminophen from OSDrC. The thickness of outer layer was (●) 0.5 mm, (▲) 1.0 mm, and (■) 2.0 mm [83].

The upper and side layers are added to form a whole tablet after the third compression.

OSDrC is applicable in controlled release formulation. It has the flexibility of including multiple cores with any shapes and varying the position of those cores. The inner core and outer layer can be formulated in a specific way to achieve a desired release profile such as sustained release, delayed and pulsatile release, or delayed and sustained release. Ozeki et al. have demonstrated that the delay time of a dry-coated acetaminophen tablet is dependent on the thickness of the outer hypromellose layer [83]. As shown in Figure 16.12, the thickest coating, 2.0 mm, has a lag time of 4.5 h whereas the 0.5 mm thick coating shows a nearly immediate release.

One-step dry-coated tablets have been applied in preparing a colonic delivery system for 5-fluorouracil (5-FU) with the mixture of Eudragit L100-55 and chitosan as the outer layer. It was shown by *in vitro* that the outer layer provided a sufficient delay for the colonic delivery of 5-FU [84].

16.6 NEW MATERIALS FOR ORAL CONTROLLED RELEASE

The advancement of oral controlled release relies not only on the invention of novel processes but also on the development of new materials. New materials with superior thermal stability are more desirable for formulation development using melt extrusion and injection molding. Novel excipients having unique hydration or erosion behavior may provide flexibility for crafting various release modes. However, the progress of new material invention is less significant than that of new processes innovation. The introduction of a material with new chemical entity is as challenging as the development of a new drug. It needs substantial safety data to pass the huge regulatory hurdle. On the other hand, pharmaceutical industry is reluctant to accept new materials to their commercial products if the performance is not superior and the usage is not necessary. Improvement of existing materials through physical changes is a more popular option.

Major excipient vendors like Dow, BASF, ISP, and FMC biopolymer are key players in innovating new material for oral controlled release. Their main strategy is to improve their flagship products in the aspect of particle size, compressibility, flow properties, and easiness of use. Ethylcellulose is widely used as a film coating agent for controlled release. Its regular grade is usually granular with the average particle size of 250 μm. Dow has developed a micronized version of ethylcellulose, called Ethocel FP. It can be used for the formulation of matrix tablets by direct compression. A direct compression grade of Methocel has also been developed by Dow to improve flow and eliminate the wet granulation step. A type of very low viscosity hypromellose, Methocel VLV from Dow, has been introduced for high productivity tablet coating applications. Kollidon SR, a combination of polyvinyl acetate and polyvinyl pyrrolidone, is desirable for direct compressed and nonerodible tablets. Kollidon SR has high dry binding capacity, which is suitable for developing porous floating systems.

There are interests in using modified starches as controlled release agents. Starch is a polysaccharide carbohydrate consisting of a large number of glucose monosaccharide. Starch is a main nutrient for human and a common pharmaceutical excipient. It is a multifunctional excipient in tablet and capsule formulations. Starch can work as a binder, disintegrant, lubricant, or flow aid. Many researches have showed that modified starch can be used as a hydrophilic polymer for matrix tablets. High-amylase carboxymethyl starch is formed by chemically modifying hydroxyl group of amylase by an etherification process. Both high-amylase carboxymethyl starch and high-amylase sodium carboxymethyl starch are suitable for developing matrix tablets [85–87]. High-amylose sodium carboxymethyl starch, produced by spray drying, was shown to have desirable properties as sustained drug release tablet excipient for direct compression. A cross-linked high amylase, Contramid, developed by Labopharm, is claimed to be desirable for developing controlled release formulations with high drug loading. Contramid is a free-flowing, highly compressible powder. A long-lasting, uniform surface membrane is formed after contramid is wetted, which helps control the release of orally administered drugs under a broad range of in-body conditions. Highly substituted starch acetate has been also introduced as a matrix-forming excipient for oral controlled delivery [88]. Release profile from the tablets could be easily adjusted over a very wide range for various drugs.

On the other hand, there are ongoing efforts in exploring some natural food ingredients as controlled release agents. Mucilage from *Hibiscus rosasinensis* Linn, a hydrophilic excipient, has been demonstrated to be applicable for the development of sustained release tablets [89]. Pectin and alginate are natural polysaccharides and have been used in food and beverage industries for many years. Pectin and alginate tend to form a complex with metal ions. The complex can be used as a matrix or membrane for the controlled delivery of drugs [90]. It has been reported that wax materials such as Dynasan 118 can be used a matrix-forming excipient. Cellulose acetate, an acetate ester of cellulose fiber, has been introduced as a pharmaceutical ingredient by Eastman Kodak. Cellulose acetate used to be a key ingredient for film base and magnetic tape. Data from Eastman Kodak suggest that cellulose acetate can be used as a controlled release agent for matrix tablets.

16.7 SUMMARY

As discussed in above paragraphs, oral controlled release is being advanced in many frontiers. New technologies such as melt extrusion, injection molding, printing technologies, and dry coating provide a great opportunity and flexibility for formulation scientists to design and develop oral controlled release formulations. Controlled release delivery of poorly soluble compounds could be pursued through several approaches with combination of solubilization and release modification. New formulation designs together with computer modeling help to achieve desired release profiles for drugs with different properties. Early promises have been shown for oral delivery of proteins and vaccines. It is optimistic that oral dosage form of biopharmaceuticals including proteins, peptides, vaccines, and nucleotides will become a reality eventually with the advancement of new technologies and new materials.

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